REVIEW

Pulmonary arterial hypertension: classification, diagnosis and contemporary management

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Positioned between the two sides of the heart and residing within the lungs, the pulmonary circulation has a central role in cardio-pulmonary gas exchange and oxygen transport. Its central position also renders the pulmonary circulation prone to injury as a result of disorders affecting the heart, lungs or systemic circulation. An uncommon, but serious and potentially devastating chronic disorder of the pulmonary circulation is pulmonary hypertension, a haemodynamic abnormality of diverse aetiology and pathogenesis. Over the past decade, several advances have occurred in the understanding, classification and medical management of pulmonary hypertension.¹ This article outlines the approach to the diagnosis of pulmonary arterial hypertension (PAH) and discusses the use of currently available drug treatments and surgical procedures for this condition.

METHODS

We searched the Cochrane Controlled Trials Register, PubMed and Medline (MESH terms: primary pulmonary hypertension *and* pulmonary arterial hypertension) for clinical trials, randomised controlled trials, meta-analyses, practice guidelines and reviews. We selected only studies on humans and articles written in English.

CLASSIFICATION

Pulmonary hypertension was previously divided into primary and secondary categories; primary pulmonary hypertension described an idiopathic hypertensive vasculopathy exclusively affecting the pulmonary circulation, whereas secondary pulmonary hypertension was associated with a causal underlying disease process. The recent identification of a gene responsible for the inherited forms of this disease, along with the development of specific medical treatments and the refinement of surgical techniques, has prompted a revised classification of pulmonary hypertension. This classification distinguishes conditions that directly affect the pulmonary arterial tree from those primarily affecting the pulmonary venous system or respiratory structure and function² (box 1). The term primary pulmonary hypertension has now more accurately been replaced by idiopathic PAH, or, when supported by genetic investigation, familial PAH; the term secondary pulmonary hypertension has been abandoned.

DEFINITION

Although there is no universally agreed definition of PAH, the generally accepted haemodynamic criteria consist of a sustained elevation

in mean pulmonary arterial pressure of >25 mm Hg at rest or 30 mm Hg after exercise, in the absence of raised left-sided cardiac pressures.³

PATHOGENESIS

In the pulmonary circulation, there is a homeostatic balance between a variety of mediators that influence vascular tone, cellular growth and coagulation. In PAH, pulmonary endothelial cell dysfunction or injury promotes the pathological triad of vasoconstriction, cellular proliferation and thrombosis through the action of mediators such as thromboxane A₂, endothelin-1 and serotonin. Under normal circumstances, these effects are counterbalanced by prostacyclin, vasoactive intestinal peptide and nitric oxide, which tend to have opposite effects.⁴ As shown in box 1, a variety of genetic and environmental triggers may lead to the endothelial cellular injury which promotes vasoconstriction, cellular proliferation and thrombosis, characteristic of PAH. Irrespective of the underlying aetiology of PAH, the histological appearance of lung tissue in each of these conditions is similar and consists of intimal fibrosis, increased medial thickness, pulmonary arteriolar occlusion and plexiform lesions.

CLINICAL PRESENTATION

Although PAH may be asymptomatic in its early stages, exertional dyspnoea is the most frequent presenting symptom and occurs virtually in all patients as the disease progresses. Fatigue and weakness are also common and a minority of patients may report angina or syncope. As PAH may be associated with a variety of conditions, evidence of a related illness should be considered. Orthopnoea and paroxysmal nocturnal dyspnoea are suggestive of pulmonary congestion due to left-sided heart disease. Raynaud's phenomenon, arthralgias and non-specific systemic symptoms should raise the possibility of an underlying connective tissue disorder. A history of snoring or apnoea warrants evaluation for sleep-disordered breathing. The appearance of peripheral oedema and abdominal distension indicate advanced disease with the development of right ventricular dysfunction and tricuspid regurgitation. Classical physical signs of PAH include a loud pulmonary component of the second heart sound and the presence of a left parasternal heave suggestive of right ventricular hypertrophy. The murmurs of pulmonary and

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Abbreviations: ECG, electrocardiography; PAH, pulmonary arterial hypertension

Box 1: Classification of pulmonary arterial hypertension

- Group 1: Pulmonary arterial hypertension (PAH)
 - Idiopathic
 - Familial
 - Associated conditions—for example, collagen vascular disease, congenital heart disease with systemic to pulmonary shunts, HIV infection, drugs and toxins, others
 - Associated with considerable capillary involvement—for example, pulmonary veno-occlusive disease, pulmonary capillary haemangiomatosis
 - Persistent pulmonary hypertension of the newborn
- Group 2: Pulmonary hypertension with left heart disease
 - Left-sided atrial, ventricular or valvular disease such as left ventricular systolic and diastolic dysfunction, mitral stenosis and mitral regurgitation
- Group 3: Pulmonary hypertension secondary to lung diseases and/or chronic hypoxaemia
 - Chronic obstructive pulmonary disease
 - Interstitial lung disease
 - Sleep-disordered breathing
 - Chronic high-altitude exposure
 - Developmental abnormalities
- Group 4: Pulmonary hypertension due to chronic thrombotic/embolic disease
 - Thromboembolic obstruction of proximal/distal pulmonary arteries
 - Non-thrombotic pulmonary embolism (tumour, parasites, foreign material)
- Group 5: Miscellaneous
 - Lymphangiomatosis as a result of widespread carcinoma, sarcoidosis, pulmonary vascular compression

tricuspid regurgitation and signs of right ventricular failure indicate advanced disease. Other physical signs—for example, finger clubbing in the case of cyanotic congenital heart disease—may provide insights into the underlying aetiology.

DIAGNOSTIC EVALUATION

Figure 1 summarises the diagnostic algorithm for PAH. Electrocardiographic (ECG) signs of the right heart compromise include right axis deviation, right ventricular hypertrophy and peaked p waves. However, the ECG lacks sufficient diagnostic accuracy to serve as a screening tool for the detection of PAH. Although the chest x ray may disclose abnormal anatomic features due to PAH and its potential causes, it is usually normal in those without symptoms. The most useful and accessible imaging modality for diagnostic purposes is echocardiography,⁵ providing a quantitative estimate of pulmonary arterial pressure and assessment of associated anatomical abnormalities such as right ventricular enlargement. Once the presence of PAH is confirmed, investigations should be aimed at identifying an

underlying cause. Echocardiography provides the benefit of being able to exclude considerable left heart disease and congenital heart disease and guiding the need and timing of cardiac catheterisation. Chronic thromboembolic pulmonary disease is a potentially curable condition that should be considered in all patients with unexplained PAH. Ventilation-perfusion scanning should be performed to rule out the condition, as a normal scan effectively excludes the diagnosis.⁶ Pulmonary function testing and arterial blood gas sampling should be carried out to check for underlying chronic airway or parenchymal lung disease. However, it should be borne in mind that even about 20% of patients with idiopathic PAH or chronic pulmonary thromboembolic disease have a restrictive defect (lung volumes <80% of predicted). If PAH remains unexplained, serological testing for connective tissue disease and HIV infection should be carried out. Although PAH has been described in all of the connective tissue disorders, it occurs most commonly in systemic sclerosis and mixed connective tissue disease, affecting 15–20% of cases.⁷ HIV infection is associated with an increased prevalence of PAH of up to 1 in 200 cases.⁸ Notably, PAH also occurs in other diseases such as sickle-cell disease, and chronic liver and renal disease. Ingestion of appetite suppressants, tryptophan and contaminated rapeseed oil have all been associated with the development of PAH. Because of its inherent risks, lung biopsy is not recommended unless diagnosis can be made by only histological examination. Right heart catheterisation remains the gold standard for assessment of pulmonary haemodynamics by providing direct and accurate measurements of pulmonary arterial pressure, pulmonary vascular resistance and cardiac output.

The absence of identifiable secondary causes of PAH should prompt the need for genetic testing. Mutations in the bone morphogenetic protein receptor II gene have been identified in approximately 50% of patients with a familial history of PAH and 25% of patients thought to have sporadic idiopathic PAH.⁹ Familial PAH is inherited in an autosomal dominant manner with incomplete penetrance of 10–20%. The age of onset of familial PAH is broad, ranging from 1 to 74 years. Genetic testing is usually performed in families with PAH in whom a specific bone morphogenetic protein receptor II mutation has previously been identified. A subject who possesses this mutation has a 10–20% risk of developing familial PAH, whereas in case of absence of the mutation, the risk is no different from the general population. Patients with idiopathic PAH should be advised about the availability of genetic testing and counselling for their relatives.

NATURAL HISTORY

Symptomatic status and the 6-min walk test are predictive of survival. An absence of symptoms or mild symptoms with normal activity is associated with a mean survival of 5 years, whereas moderate symptoms preventing normal activity or symptoms at rest are associated with a mean survival of 2.5 years and 6 months, respectively.¹⁰ If left untreated, PAH is characterised by a progressive increase in pulmonary vascular resistance leading to worsening right ventricular function and death.

GENERAL TREATMENT MEASURES

General treatment measures for PAH should be considered after the identification of any underlying associated disorders or contributing factors (fig 2). Although these treatments (calcium channel blockers, warfarin, supplemental oxygen, diuretics and digoxin) are not supported by randomised controlled trials, they are widely used in the management of PAH and are generally accepted as being important and efficacious.

Figure 1 Diagnostic evaluation of pulmonary arterial hypertension (PAH).

Intense vasodilator testing is central to formulating the treatment strategies for idiopathic PAH, the primary objective being to delineate those who show considerable reductions in pulmonary arterial pressure (defined as a fall in mean

pulmonary arterial pressure of at least 10 to ≤ 40 mm Hg, with an increased or unchanged cardiac output) and might effectively be treated with oral vasodilating drugs.¹¹ The principle of intense vasodilator testing and treatment was

Figure 2 Algorithm for the treatment of pulmonary arterial hypertension (PAH).

established by an early report which showed that oral diazoxide improved clinical symptoms and cardiopulmonary haemodynamics when given to those with a positive response to injections of diazoxide directed into the main pulmonary trunk.¹² After a number of clinical studies since then, short-acting vasodilators in the form of either intravenous epoprostenol¹³ or inhaled nitric oxide are now the preferred agents for vasodilator testing. In addition, based on therapeutic studies in PAH over the past two decades, patients who show a remarkable response to vasodilator testing are given oral calcium channel blockers as first-choice vasodilating drugs. In a prospective non-randomised study, Rich *et al*¹⁴ showed that 17 patients with a favourable good vasodilator response had a 94% 5-year survival rate when treated with high-dose calcium channel blockers compared with a 38% 5-year survival rate in 47 patients classified as non-responders to intense vasodilator testing. Nifedipine, amlodipine or diltiazem may be given, and the choice could be based on the baseline heart rate. Verapamil should be avoided because of its negative inotropic effect. In general, the use of calcium channel blockers should be monitored closely to determine both the safety and efficacy of treatment. Calcium channel blockers should not be used empirically to treat PAH in the absence of proved vasoreactivity, and should be avoided in unstable patients or those with severe right heart failure.

Microscopic thrombosis has been shown in some patients with idiopathic PAH. In addition, patients with right ventricular failure and venous stasis are at an increased risk for pulmonary thromboembolism. Consequently, improved survival has been reported with oral anticoagulation in patients with idiopathic PAH.¹⁴ When considering long-term anticoagulation in patients with PAH, the risk:benefit ratio should be carefully taken into account. In general, patients with PAH receiving treatment with long-term intravenous epoprostenol (discussed below) should be anticoagulated in the absence of contraindications, partly because of the risk of catheter-related thrombosis.

As hypoxaemia is a potent pulmonary vasoconstrictor, supplemental oxygen should be used as necessary in patients with idiopathic PAH to maintain oxygen saturations at >90% at all times. Diuretics and digoxin may be given in patients with right heart failure, and respiratory tract infections should be treated aggressively.

NEWER DRUG THERAPIES

Patients with moderate to severe limitation of physical activity unresponsive to calcium channel blockers should be considered for long-term treatment with more specialised treatments such as prostacyclin analogues or endothelin receptor antagonists (fig 2). In contrast with the treatments described in the previous section, the efficacy of these more specific treatments is supported by a limited number of randomised controlled trials.

Prostacyclin analogues

There is evidence to suggest that a relative deficiency of prostacyclin, a potent vasodilator with antiplatelet effects, may contribute to the pathogenesis of PAH.⁴ Consequently, recent studies have investigated the possibility that prostacyclin analogues might be of long-term benefit to patients with moderate or severe PAH. Randomised, controlled, open-label trials of the intravenously administered prostacyclin analogue, epoprostenol, have shown a beneficial effect on exercise capacity, haemodynamics and quality of life in patients with moderate to severe PAH.^{15–16} In addition, a recent report of long-term epoprostenol therapy in 162 consecutive patients with idiopathic PAH followed up for an average of 3 years observed a 3-year survival rate of 63%

compared with the expected survival of 35% based on historical data.¹⁷ However, the use of epoprostenol is complicated by the need for continuous intravenous infusion, causing inconvenience to the patient and increasing the risk of systemic infection and venous thrombosis. The drug is unstable at room temperature and has a very short half life of <6 min in the bloodstream. Common side effects include headache, flushing, jaw pain, nausea and rash; because of its short half life, abrupt cessation of treatment can also cause a rebound worsening of PAH in some patients.

The requirement for constant intravenous infusion of epoprostenol has led to the development of prostacyclin analogues with alternative routes of delivery. Treprostinil is a prostacyclin analogue which is stable at room temperature, has a half life of 3 h and can be given subcutaneously. The use of treprostinil has shown improvements in exercise capacity and haemodynamics similar to intravenous epoprostenol.^{18–19} However, a significant problem associated with treprostinil is pain and erythema at the infusion site, making administration of the target dose of the drug difficult to achieve.

The use of the inhaled prostacyclin analogue, iloprost, is an attractive alternative option that has been applied to clinical practice and, based on available data, appears to be a safe, effective and well-tolerated treatment for severe PAH.²⁰ A 3-month, randomised, double-blind, placebo-controlled trial in 203 patients with PAH showed significant beneficial effects on symptoms status, exercise capacity and haemodynamics.²¹ Inhaled iloprost is generally well tolerated, but its main drawback is the relatively short duration of action requiring the use of 6–9 inhalations/day.

Beraprost is the latest in the line of prostacyclin analogues and the first orally acting agent. It is an approved therapy for PAH in Japan and is currently under evaluation in Europe.²²

Endothelin receptor antagonists

Endothelin receptor antagonism is a promising therapeutic approach supported by increasing evidence of the pathogenic role of endothelin-1 in PAH. Endothelin-1 is a potent vasoconstrictor that might contribute to the increase in vascular tone and the pulmonary vascular hypertrophy associated with PAH.^{4–23–24} Plasma levels of endothelin-1 are correlated with exercise capacity, haemodynamics and disease severity.²⁵ The endothelin receptor antagonists, bosentan and sitaxsentan, have undergone randomised, double-blind, placebo-controlled clinical trials in moderately to severely symptomatic patients with PAH. Both drugs have shown improvements in exercise capacity and haemodynamics after 3–4 months of treatment.^{26–29} Both drugs also have the advantage of oral administration with sitaxsentan owing to superior oral bioavailability and a longer duration of action. However, side-effects, including syncope and flushing, are common; in addition, the drugs should be administered cautiously because of a dose-dependent increased risk of hepatotoxicity and important drug interactions.³⁰

Phosphodiesterase inhibitors

Several phosphodiesterase inhibitors, including dipyridamole, cause potent pulmonary vasodilatation in animal models of acute and chronic PAH.^{31–32} Early clinical studies showed that dipyridamole could reduce PAH. However, in practice, its use has been limited by the lack of potency and selectivity and systemic side effects.³³ Several reports of non-randomised single-centre studies using the phosphodiesterase inhibitor sildenafil for the treatment of PAH suggest this agent to be promising, with relatively few side effects.^{34–35} Sildenafil has been shown to block acute hypoxic pulmonary vasoconstriction in healthy volunteers and improve exercise capacity and pulmonary artery pressure in

patients with PAH. However, randomised controlled trials are needed to compare the efficacy of sildenafil with those of other agents and evaluate its role in combination therapy.

The use of combination therapies with different mechanisms of action has not been formally evaluated in clinical trials.

SURGICAL TREATMENT

The advances in medical therapies have overshadowed the role of surgical interventions. The rationale for surgical therapies in PAH is based on the identification of subsets of patients in whom a specific procedure is indicated. The three main forms of surgical treatment are atrial septostomy, pulmonary thromboendarterectomy and lung transplantation. The aim of atrial septostomy is to create a right to left shunt to decompress the right ventricle and increase systemic blood flow. This procedure was introduced following the observation that patients with PAH and a patent foramen ovale awaiting transplantation had a survival advantage over those without a patent foramen ovale. However, the procedure carries significant periprocedural morbidity and mortality, limiting its use to patients with severe PAH unresponsive to medical treatment, and requiring palliation or a bridge to transplantation.^{36–38} Pulmonary

thromboendarterectomy may be indicated in patients with chronic pulmonary thromboembolism with moderate to severe symptoms, raised pulmonary vascular resistance, surgically accessible thrombus and no major comorbidities.³⁶ However, great care must be taken in the appropriate selection of candidates for this technique as procedural mortality can be high.³⁹ The use of prostacyclin analogues has reduced the need for lung transplantation. In the current era, transplant surgery should not be considered until after the failure of medical therapy.³⁶

CONCLUSIONS

The past decade has seen major advances in our understanding of the pathophysiological mechanisms underlying the development of PAH. The diagnosis is now more clearly defined according to a new clinical classification, and clear algorithms have been devised for the investigation of PAH. A number of controlled clinical trials have shown benefit of newer drug therapies such as prostacyclin analogues, endothelin receptor antagonists and phosphodiesterase inhibitors, and these advances in medical therapy have limited the role of surgical interventions. However, the complexity of the treatment options and the relatively rare occurrence of the disease necessitate referral to a specialist centre. Further research into the underlying mechanisms of disease and the evaluation of novel treatment modalities should lead to continued improvements in the management of this condition.

Summary points

- Pulmonary arterial hypertension (PAH) is an uncommon condition which may be idiopathic, familial or associated with a variety of underlying disorders including chronic lung disease, chronic pulmonary thromboembolism or connective tissue disease.
- Echocardiography is a useful screening tool for the detection of pulmonary arterial hypertension, providing a quantitative estimate of pulmonary arterial pressure and an assessment of associated or underlying anatomical abnormalities.
- Patients with idiopathic PAH should be referred to a specialist centre and commenced on treatment with oxygen, diuretics, digoxin and anticoagulation.
- Acute vasodilator testing has a central role in identifying those who might benefit from treatment with calcium channel blockers.
- Specialised treatment with prostacyclin analogues and endothelin antagonists should be considered in those with moderate to severe symptoms unresponsive to calcium channel blockers.

Additional educational resources

Clinical guidelines

Guidelines on diagnosis and treatment of pulmonary arterial hypertension. The task force on diagnosis and treatment of pulmonary arterial hypertension of the European Society of Cardiology. *Eur Heart J* 2004;**25**:2243–78.

Useful websites for patients

Pulmonary Hypertension Association. www.pha-uk.com.
British Heart Foundation. www.bhf.org.uk
National Heart Lung and Blood Institute. www.nhlbi.nih.gov
The Cochrane Library. www.nelh.nhs.uk
Find Articles. www.findarticles.com

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